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Rethinking ARDS classification: oxygenation impairment fails to predict VILI risk

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Abstract

Purpose: The selection and intensity of respiratory support for ARDS are guided by PaO_2/FiO_2. However, ventilator-induced lung injury (VILI) is linked to respiratory mechanics and ventilator settings. We explored whether the VILI risk is related to ARDS severity based on oxygenation.

Methods: We analysed data on 228 ARDS subjects with $PaO_2/FiO_2 < 200$ mmHg, categorized into three severity groups: one based on PaO_2/FiO_2 ratio, and the others based on tertiles of predictors of VILI: mechanical power ratio (MPR) and driving pressure (DP). In each group of oxygenation-based ARDS severity and MPR and DP tertiles, we measured CT anatomy, gas exchange, respiratory mechanics, VILI prerequisites (lung elastance and lung gas volume), and VILI determinants (tidal volume, PEEP, airway pressures).

Results: Predictors of VILI, such as MPR and DP, were similar across ARDS severity groups based on PaO_2/FiO_2 ratio, while oxygenation remained comparable across different levels of VILI risk defined by MPR and DP. Oxygenation impairment was associated with increased lung weight, recruitability, and reduced well-inflated tissue. In contrast, MPR and DP tertiles affected variables associated with the baby lung size, such as lung gas volume and well-inflated tissue. Mechanical ventilation intensity increased progressively across MPR and DP tertiles, but remained similar across PaO_2/FiO_2 severity groups.

Conclusions: ARDS severity based on oxygenation impairment does not reflect the prerequisites and determinants of VILI. This should prompt a reconsideration of recommending respiratory support based on oxygenation impairment, rather than VILI determinants.

Keywords: ARDS severity, Mechanical power, Respiratory mechanics, Ventilator-induced lung injury, Gas exchange

Introduction

The definition of acute respiratory distress syndrome (ARDS) and its severity criteria have changed over the years. The original description [1] included oxygenation, respiratory mechanics, imaging, and anatomical alterations. However, the Berlin definition [2] later excluded respiratory mechanics, as did the more recent proposal of the "global ARDS definition" [3]. Notably, CO_2-related variables have never been included in the ARDS definition or in assessing its severity, and the central criterion for ARDS definition remains the oxygenation.

Consequently, guidelines for managing ARDS base their recommendations on the severity of the oxygenation defect, suggesting that a lower PaO_2/FiO_2 ratio

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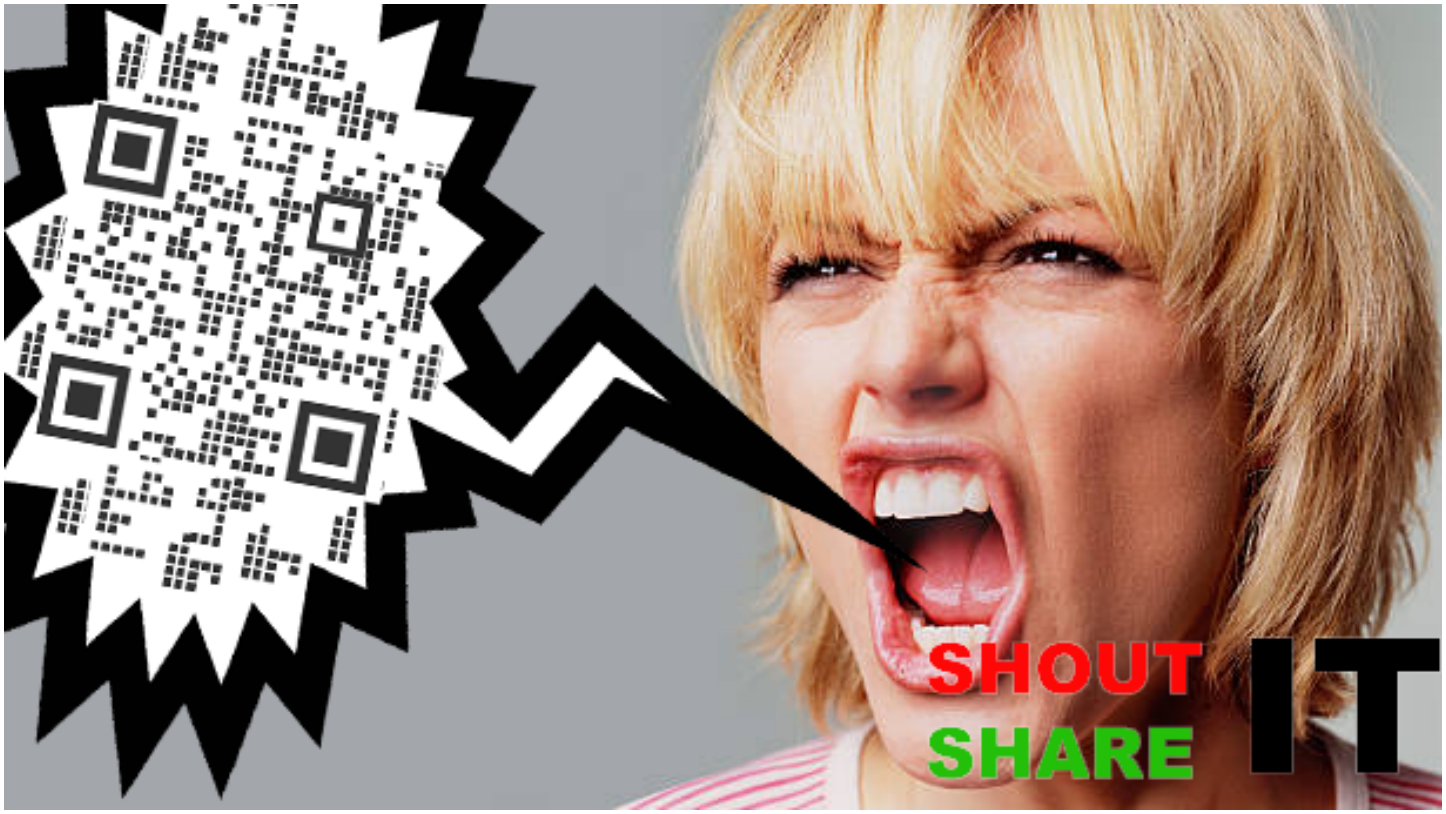
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(P/F) requires more complex and intensive therapy [4]. Indeed, as the oxygenation impairment becomes more severe (with traditional P/F thresholds of 300, 200, and 100 mmHg for mild, moderate or severe categories), the intensity of respiratory support is presumed to increase. This applies to therapies such as higher positive end-expiratory pressure (PEEP), prone position, or extracorporeal support (supplementary figure S1) [4].

It is important to recognize that respiratory support does not cure ARDS. Rather, it maintains gas exchange, buying time for the underlying cause of ARDS to resolve. Despite the emphasis on the P/F ratio, maintaining adequate oxygenation is generally not the main challenge, as most patients can maintain sufficient PaO_2 and rarely die from hypoxaemia. The real problem lies in the "cost" of ventilation, and the associated damage to the lung parenchyma, referred to as ventilator-induced lung injury (VILI). The risk of VILI is not directly linked to oxygenation (except perhaps in cases of high FiO_2), but rather with the power of ventilation required to move gas for a given respiratory system mechanics. In other words, VILI derives from the excessive unphysiological cumulative stress and strain over time caused by mechanical ventilation.

We hypothesize that the risk of VILI is determined by the interaction between anatomical factors—measured by computed tomography (CT) as "susceptibility variables"—and external factors, specifically the type and settings of ventilation. VILI risk arises from the interplay between these susceptibility factors and the mechanical forces applied during ventilation. For instance, tidal volume is an injury-inducing factor, but its impact depends on the lung's susceptibility, such as aerated lung volume. The true determinant of VILI is the ratio of tidal volume to lung volume (strain), which reflects this interaction. Similarly, added pressure interacts with lung elastance to determine lung stress, another key VILI determinant. Driving pressure and mechanical power also determine VILI by reflecting the relationship between external mechanical factors and the lung's compliance. The mismatch between the mechanical load and the lung's capacity defines the injury risk, with higher mechanical power or driving pressure (or stress and strain) leading to a greater risk of adverse outcomes.

In this framework, oxygenation is linked to certain anatomical features, but not directly to other factors involved in VILI. Since oxygenation is influenced by vascular and perfusion factors, its relationship with VILI elements is unreliable. Thus, low oxygenation, often seen in severe ARDS, does not necessarily increase VILI risk if the defect is mainly vascular (e.g. in coronavirus disease 2019 (COVID-19) [5]), highlighting a potential uncoupling between oxygenation-based classifications and the true determinants of VILI.

Take-home message

Guidelines recommend intensity of respiratory support based on PaO_2/FiO_2 severity thresholds; however, the respiratory mechanical properties and ventilatory setting (prerequisites–determinants of ventilator-induced lung injury) are mostly unrelated to oxygenation impairment. Therefore, tailoring respiratory support on oxygenation is questionable.

In this study, we investigated the relationship between gas exchange variables, respiratory mechanics, and anatomical data deriving from quantitative CT scan of moderate and severe ARDS patients with a P/F ratio < 200 mmHg. The aim of this study is to evaluate whether oxygenation and mechanical variables are sufficiently correlated to justify the current guidance of basing therapy intensity on oxygenation criteria. If, as we hypothesize, they are not, then the existing paradigm for determining therapy intensity may need to be re-evaluated in favour of variables associated with intensity of ventilation and risk of VILI.

Methods

Study population

The study population included 228 patients with ARDS, enrolled between May 2003 and July 2024, from San Paolo University Hospital of Milan (Italy), Universitatmedizin Center Goettingen (Germany), Ospedale Maggiore Policlinico of Milan (Italy), Azienda Ospedaliera San Gerardo Monza (Italy) and Pontificia Universidad Catolica de Chile (Chile) (See Supplement, Methods section). Patients were classified based on their severity. For clarity, in this manuscript we excluded patients with mild ARDS and COVID-19 aetiology, as their characteristics and outcomes may differ significantly from those with moderate and severe ARDS. We will then focus on three groups of ARDS: Mild–Moderate, including patients with a P/F ratio 200–151 mmHg; Moderate–Severe, with a P/F ratio 150–101 mmHg; and Severe, with a P/F ratio ≤ 100 mmHg [6].

VILI predictive variables

To quantify the possible harm associated with mechanical ventilation, we used two variables: the driving pressure (DP) and the mechanical power ratio (MPR). The DP was defined as

$$\text{Driving pressure} = \text{plateau pressure} - \text{PEEP}.$$

The mechanical power (MP) was computed as

$$\mathrm{MP} = 0.098 \times \mathrm{RR} \times \left\{ V_T^2 \times \left[\frac{1}{2} \times E_{\mathrm{rs}} + \mathrm{RR} \times \frac{1 + I:E}{60 \times I:E} \times R_{\mathrm{aw}} \right] + V_T \times \mathrm{PEEP} \right\},$$

where RR is the respiratory rate, V_T the tidal volume, E_{rs} the respiratory system elastance, *I:E* the ratio of the inspiratory time to the expiratory time, R_{aw} the airways resistance, and PEEP the positive end-expiratory pressure. The mechanical power ratio was computed as the ratio of the actual mechanical power to the expected normal mechanical power, as previously reported [7], assuming the following normal values for the variables involved:

Respiratory rate = 15 bpm,

Tidal volume $= \frac{0.1\,(l \cdot \mathrm{min}^{-1}) \times \mathrm{IBW(kg)}}{\text{respiratory rate}}$, where the IBW is the ideal body weight, and 0.1 l/min is the expected normal minute ventilation per kg, as in the ventilatory ratio computation [8].

The E_{rs}, the inverse of the respiratory system compliance ($1/C_{\mathrm{rs}}$), was derived assuming a linear relationship between compliance and lung gas volume. Thus, we assumed that 2.5 l of functional residual capacity (FRC) in a heathy subject would result in a respiratory system compliance of 80 ml/cmH_2O, i.e. respiratory system elastance of 12.5 cmH_2O/l. Therefore, the ideal respiratory system elastance ($\mathrm{Ers_{ID}}$) of a subject with a different FRC was computed according to the following proportion (see Supplement for the derivation):

$$E_{\mathrm{rsID}} = \frac{2.5l}{\mathrm{FRC_{ID}} \cdot 0.08l \cdot \mathrm{cmH_2O}^{-1}}.$$

The ideal FRC ($\mathrm{FRC_{ID}}$) was computed according to the Ibañez equation [9], expressed in litres:

$$\mathrm{Men}: \mathrm{FRC} = 5.48\mathrm{height} - 7.05;\ \mathrm{women}: \mathrm{FRC} = 1.39\mathrm{height} - 0.424.$$

with the height expressed in metres. We also assumed an I:E ratio of 1:2 (i.e. 0.5), normal airways resistance including the endotracheal tube of 10 cmH_2O/l/s, and a PEEP of 0 cmH_2O.

Thus, the final formula to calculate the expected MP is as follows:

$$\mathrm{MP_{expected}} = 1.47 \times V_T^2(l) \times \left(\frac{0.015625}{\mathrm{FRC_{ID}}(l)} + 0.5 \times \mathrm{RR(bpm)} \right).$$

We normalized the mechanical power to its expected value as mechanical power per se is an extensive property of the system, i.e. it depends on the dimension of the respiratory system, while the driving pressure is an intensive property, not depending on the system dimension (See Supplement, Methods section).

The following variables were collected:

- *Anthropometric and demographic characteristics*.
- *CT scan variables*. These were measured at standard conditions using 5 and 45 cmH_2O of continuous positive airway pressure (CPAP). Lung weight and lung gas volume, fraction of overinflated, well-, poorly, and not-inflated tissue, and recruitability were calculated using standard methods [10].
- *Gas exchange variables*. PaO_2, FiO_2, P/F ratio, $PaCO_2$, ventilatory ratio.
- *Respiratory system variables*. Respiratory lung and chest wall elastances, stress (plateau pressure times the ratio of lung elastance to the respiratory system elastance), strain, (calculated as the ratio of tidal volume plus PEEP volume to the CT scan-derived FRC volume [i.e. end-expiratory gas volume at 5 cmH_2O of PEEP minus PEEP volume]), and minute ventilation.

Gas exchange and respiratory system variables were collected at baseline in clinical conditions (after intensive care unit admission and initial patient stabilization); blood gas analysis and collection of respiratory mechanics was performed concurrently.

Population stratification. The patient population was then divided into the following groups.

1) Three ARDS $\mathrm{severity_{P/F}}$ groups: Mild–Moderate, Moderate–Severe, and Severe [6].;
2) Three increased mechanical power ratio groups based on tertiles with equal number of subjects of MPR: ARDS $\mathrm{severity_{MPR}}$ (Low, Mid, High).
3) Three increased driving pressure groups based on tertiles with equal number of subjects of DP: ARDS $\mathrm{severity_{DP}}$ (Low, Mid, High).

Statistical analysis

Continuous variables are presented as mean and standard deviation. Linear regression was used to assess the relationship between continuous variables. A p value of < 0.05 was considered as statistically significant. Analysis and figures were prepared using RStudio (RStudio Team 2020; RStudio: Integrated Development for R. RStudio, PBC, Boston, MA, URL http://www.rstudio.com/).

Results

In Fig. 1, we show the predictors of VILI (MPR and DP) as a function of ARDS severity$_{P/F}$. These variables were similar across the severity groups based on oxygenation efficiency. In Fig. 2, we show individual P/F ratios as a function of tertiles of MPR and DP, where P/F is similar across the increasing tertiles of MPR and DP.

In Table 1, we present the distribution of several variables across the ARDS severity$_{P/F}$ classes and tertiles of MPR and DP. The table is composed of five blocks including CT anatomy, gas exchange, respiratory mechanics, VILI determinants, and demographic/illness severity data.

Lung anatomy (Table 1, block 1)

As shown, the oxygenation impairment, as defined according to the ARDS severity$_{P/F}$, was significantly associated with most of the CT-derived variables. Indeed, the lung weight and recruitability increased across the ARDS severity$_{P/F}$ reflecting a greater fraction of atelectasis in the more oedematous and heavier lung (supplementary figure S2). The oxygenation deteriorated when the not-inflated lung tissue increased, and the well-inflated lung tissue and the lung gas volume decreased. Both these last two variables reflect the size of the "baby lung" (supplementary figure S3).

In contrast, when the patients were grouped according to increased MPR and DP tertiles, the only CT-derived variables which deteriorated across the tertiles were the ones linked to the baby lung size, i.e. the total lung gas volume in both MPR and DP tertiles and well- and poorly inflated lung tissue in DP tertiles. This is well explained by the fact that the DP and MPR are applied to the open and ventilatable regions of the lung, while they cannot reach the not-inflated lung regions.

Gas exchange (Table 1, block 2)

The CT scan variables accounted only in part for the gas exchange variations. Indeed, while P/F was significantly positively related to well-inflated lung tissue and total lung gas volume, and negatively related to not-inflated lung tissue, the PaO_2 showed no such relationships (see Supplement, Figs. S4-5, S9, S11-12). This suggests that other factors, like differences in perfusion distribution, play an important role in determining gas exchange. The $PaCO_2$ was weakly and negatively related with the well-inflated lung tissue, but showed no relationship with the other anatomical variables. However, $PaCO_2$ levels increased with worsening P/F ratio severity, but showed no correlation with severity when using MP or DP criteria, although this was at the cost of a significantly higher minute ventilation. In contrast, the ventilatory ratio, as a surrogate for dead space, significantly rose with increasing severity across all classification criteria (P/F, MPR, and DP).

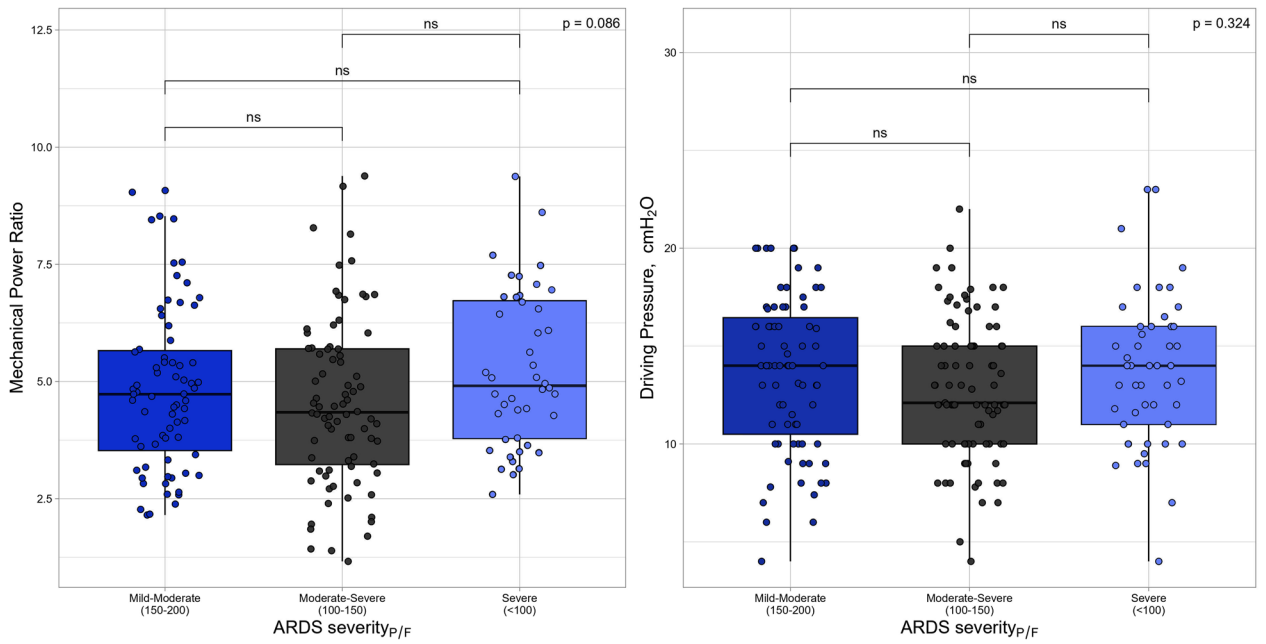

Fig. 1 Mechanical power ratio and driving pressure as a function of ARDS severity$_{P/F}$ classes. Statistical analysis was performed by one-way ANOVA or Kruskal–Wallis test as appropriate. Post hoc multiple comparisons were performed by pairwise Student's *t* test or Wilcoxon test with Bonferroni correction. At linear regression mechanical power ratio vs P/F and driving pressure vs P/F had a $p = 0.271$, $R^2 < 0.01$ and $p = 0.916$, $R^2 < 0.01$, respectively. P/F (PaO_2/FiO_2): ratio of arterial partial pressure of oxygen to the inspired fraction of oxygen

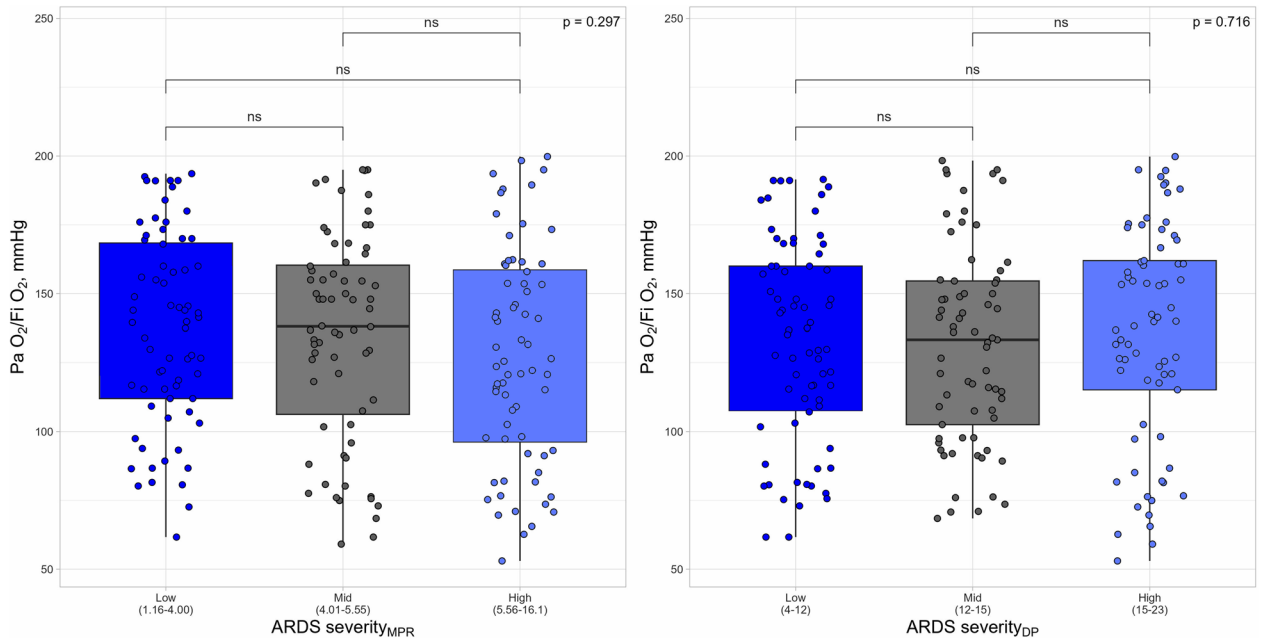

Fig. 2 PaO_2/FiO_2 as a function of mechanical power ratio and driving pressure tertiles. Statistical analysis was performed by one-way ANOVA or Kruskal–Wallis test as appropriate. Post hoc multiple comparisons were performed by pairwise Student's *t* test or Wilcoxon test with Bonferroni correction. At linear regression P/F vs mechanical power and P/F vs driving pressure had a $p = 0.271$, $R^2 < 0.01$ and $p = 0.916$, $R^2 < 0.01$, respectively. P/F (PaO_2/FiO_2): ratio of arterial partial pressure of oxygen to the inspired fraction of oxygen

Respiratory mechanics (Table 1, block 3)

Patients with different ARDS $severity_{P/F}$ had similar respiratory mechanical variables, indicating that the inspiratory pressures were linked to mechanical characteristics such as increased elastance and reduced baby lung size, rather than P/F level. Strain increased in both the more severe ARDS classes and the higher MPR and DP tertiles.

VILI determinants (Table 1, block 4)

VILI depends on the interaction between the lung status, largely determined by the underlying disease, and the ventilatory setting chosen by clinicians. As shown, the mechanical ventilation settings were similar across ARDS $severity_{P/F}$. However, as expected, mechanical ventilation was progressively more intense across the MPR and DP tertiles.

Demographic and outcome (Table 1, block 5)

In this population (P/F < 200 mmHg), there was no meaningful difference in demographic and overall illness severity across the different ARDS categories.

In summary, classification based on oxygenation did not capture the variables related to VILI, while classifications based on MPR and DP did not capture the oxygenation impairment.

Discussion

In this study, we found that classifying ARDS severity based on the P/F ratio did not lead to significant differences in respiratory mechanics, ventilatory settings, or mechanical power (MPR) and driving pressure (DP). Furthermore, patients grouped by MPR and DP tertiles showed similar P/F ratios. Across all severity classifications, as ARDS severity worsened (lower P/F ratio or higher MPR/DP), well-inflated lung tissue decreased, non-inflated tissue increased, and the ventilatory ratio, a surrogate for dead space, rose. However, ventilation demands and settings were primarily reflected in the MPR and DP classifications, while these factors remained largely unchanged across P/F-based severity classes. Although the P/F ratio is closely linked to anatomical changes and recruitability, it does not represent the determinants of VILI, resulting in similar mechanical characteristics across P/F-based severity groups.

VILI fundamentally arises from the interaction between the anatomical conditions of the lung—specifically the "baby lung" size and elastance—and the mechanical ventilator settings, including tidal volume, PEEP, and respiratory rate. Mechanical power, which accounts for both the respiratory system's elastance and the ventilatory settings, and driving pressure, which represents the product of tidal volume and elastance, are critical determinants of

Table 1 Lung anatomy, gas exchange, respiratory mechanics–VILI prerequisites, VILI determinants, and demographic data according to ARDS severity classes, mechanical power ratio tertiles, and driving pressure tertiles assessed at baseline

	ARDS severity$_{P/F}$				ARDS severity$_{MPR}$				ARDS severity$_{DP}$			
	Mild–Moderate	Moderate–Severe	Severe	*p* value	Low tertile	Mid tertile	High tertile	*p value*	Low tertile	Mid tertile	High tertile	*p* value
	PaO_2/FiO_2 200–151	PaO_2/FiO_2 150–101	PaO_2/FiO_2 ≤ 100		MPR 1.16–4.00	MPR 4.01–5.55	MPR 5.56–16.1		DP 4–12	DP 12–15	DP 15–23	
	N = 80	*N* = 99	*N* = 49		*N* = 68	*N* = 68	*N* = 68		*N* = 70	*N* = 69	*N* = 69	
Lung anatomy												
1												
Total lung tissue, g	1468 (428)	1584 (594)	1677 (554)	< 0.001	1561 (559)	1567 (502)	1583 (531)	0.102	1575 (579)	1583 (497)	1572 (510)	0.890
Overinflated tissue, %	0.37 (1.14)	0.18 (0.42)	0.15 (0.39)	0.869	0.31 (0.73)	0.38 (1.11)	0.07 (0.20)	0.060	0.48 (1.26)	0.17 (0.39)	0.11 (0.29)	< 0.001
Well-inflated tissue, %	29 (15)	22 (12)	16 (9)	< 0.001	26 (14)	24 (13)	20 (12)	0.003	27 (15)	22 (12)	21 (12)	< 0.001
Poorly inflated tissue, %	31 (12)	28 (13)	30 (12)	0.585	29 (14)	29 (11)	32 (12)	0.193	26 (13)	30 (10)	33 (13)	0.006
Not-inflated tissue, %	40 (16)	50 (16)	53 (12)	< 0.001	45 (17)	46 (16)	48 (16)	0.101	46 (19)	48 (14)	46 (17)	0.036
Total gas volume, ml	1282 (754)	1000 (499)	891 (570)	0.013	1226 (756)	1119 (592)	948 (589)	0.006	1309 (785)	1018 (564)	942 (536)	< 0.001
Recruitability, %	14 (12)	18 (13)	24 (15)	< 0.001	19 (14)	17 (16)	18 (12)	0.263	19 (15)	19 (14)	17 (13)	0.094
Gas exchange												
2												
PaO_2, mmHg	86 (18)	77 (12)	64 (12)	–	76 (13)	77 (17)	79 (20)	0.008	75 (13)	75 (14)	82 (21)	0.023
FiO_2, %	0.5 (0.1)	0.6 (0.1)	0.8 (0.1)	–	0.6 (0.1)	0.6 (0.2)	0.7 (0.2)	< 0.001	0.6 (0.1)	0.6 (0.2)	0.6 (0.2)	0.040
PaO_2/Fio_2	173 (15)	128 (13)	81 (12)	–	137 (35)	135 (38)	127 (39)	0.271	133 (37)	131 (36)	135 (40)	0.916
$PaCO_2$, mmHg	44 (9)	46 (10)	57 (21)	< 0.001	47 (9)	51 (16)	47 (16)	0.530	47 (13)	48 (14)	49 (15)	0.293
Minute ventilation, l/min	8.7 (2.5)	7.9 (2.7)	8.4 (2.2)	0.271	6.7 (1.8)	8.1 (2.0)	9.4 (2.2)	< 0.001	7.1 (2.0)	8.0 (2.1)	9.0 (2.5)	< 0.001
Ventilatory ratio	1.59 (0.48)	1.52 (0.56)	2.00 (0.91)	0.002	1.24 (0.36)	1.67 (0.53)	2.00 (0.72)	< 0.001	1.38 (0.54)	1.63 (0.65)	1.87 (0.63)	< 0.001
Respiratory mechanics–vili prerequisites												
3												
$Elastance_{RESPIRATORY\ SYSTEM}$, cmH_2O/l	28.7 (11.3)	28.1 (10.2)	30.5 (11.7)	0.258	25.8 (13.6)	27.9 (8.3)	32.5 (8.8)	–	20.1 (5.1)	29.1 (9.6)	37.5 (9.6)	–
$Elastance_{LUNG}$, cmH_2O/l	23.5 (11.4)	19.7 (7.3)	22.8 (11.0)	0.854	18.8 (12.0)	21.7 (7.3)	25.3 (8.6)	–	14.7 (5.4)	21.3 (5.0)	32.5 (10.4)	–
Peak pressure, cmH_2O	29.7 (5.9)	30.6 (6.6)	32.2 (7.0)	0.024	25.1 (3.9)	30.8 (4.6)	36.3 (5.2)	–	25.5 (4.4)	31.3 (5.3)	35.3 (5.6)	–
Plateau pressure, cmH_2O	23.6 (4.7)	22.7 (4.3)	23.7 (5.1)	0.903	20.7 (4.4)	23.3 (3.9)	25.8 (3.8)	–	19.0 (3.1)	23.9 (3.0)	27.3 (2.8)	–
Stress, cmH_2O	18.3 (4.7)	16.7 (4.8)	17.0 (5.9)	0.322	14.9 (5.7)	17.7 (3.8)	19.9 (4.3)	< 0.001	13.3 (3.9)	18.3 (3.8)	21.9 (3.0)	< 0.001
Strain	0.94 (0.64)	1.10 (0.61)	1.58 (1.21)	0.035	1.03 (0.67)	1.01 (0.68)	1.38 (1.10)	< 0.001	1.06 (0.70)	1.16 (0.84)	1.26 (1.02)	< 0.001
VILI determinants												
4												
Tidal volume per kg, ml/kg IBW	7.9 (1.8)	7.7 (1.7)	7.5 (1.4)	0.067	7.0 (1.5)	7.5 (1.2)	8.6 (1.6)	–	7.2 (1.4)	7.8 (1.7)	8.0 (1.8)	–
Respiratory rate, bpm	18 (6)	16 (4)	18 (5)	0.780	14 (3)	17 (4)	19 (5)	–	15 (3)	17 (4)	19 (5)	–

Table 1 (continued)

	ARDS severity$_{P/F}$				ARDS severity$_{MPR}$				ARDS severity$_{DP}$			
	Mild–Moderate	Moderate–Severe	Severe	*p* value	Low tertile	Mid tertile	High tertile	*p value*	Low tertile	Mid tertile	High tertile	*p* value
	PaO_2/FiO_2 200–151	PaO_2/FiO_2 150–101	PaO_2/FiO_2 ≤ 100		MPR 1.16–4.00	MPR 4.01–5.55	MPR 5.56–16.1		DP 4–12	DP 12–15	DP 15–23	
	N = 80	*N* = 99	*N* = 49		*N* = 68	*N* = 68	*N* = 68		*N* = 70	*N* = 69	*N* = 69	
Inspiratory flow, ml/s	433 (123)	394 (133)	418 (112)	0.271	335 (88)	405 (100)	470 (110)	–	356 (99)	401 (104)	448 (127)	–
PEEP, cmH_2O	10.21 (2.93)	10.23 (2.56)	9.89 (2.89)	0.670	9.39 (2.79)	10.25 (2.53)	10.10 (2.36)	0.154	9.80 (2.99)	10.48 (2.70)	9.77 (2.15)	0.525
Demographic and illsess severity												
5												
Age, years	60 (16)	60 (16)	61 (16)	0.629	61 (17)	63 (15)	60 (16)	0.219	64 (15)	59 (17)	61 (16)	0.287
BMI, kg/m^2	27 (7)	27 (6)	27 (6)	0.809	26 (5)	26 (7)	28 (7)	0.085	27 (5)	27 (8)	28 (7)	0.289
SAPS II	41 (14)	40 (16)	39 (15)	0.386	42 (16)	40 (11)	38 (15)	0.186	42 (15)	40 (13)	39 (15)	0.611

Data are expressed as mean (SD)

ARDS severity$_{P/F}$ patients grouped according to P/F severity categories, *ARDS severity$_{MPR}$* patients grouped according to tertiles of mechanical power ratio, *ARDS severity$_{DP}$* patients grouped according to tertiles of driving pressure, *ARDS* acute respiratory distress syndrome, *BMI* body mass index, *DP* driving pressure, *FiO_2* inspiratory fraction of oxygen, *IBW* ideal body weight, *MPR* mechanical power ratio, *$PaCO_2$* arterial partial pressure of carbon dioxide, *PaO_2* arterial partial pressure of oxygen, *PEEP* positive end-expiratory pressure, *P/F* PaO_2/FiO_2, *SAPS II* simplified acute physiology score II, *VILI* ventilator-induced lung injury.

While the population is represented in groups for clarity, the statistics applied refers to the linear regression between the variables vs P/F, mechanical power ratio, and driving pressure. A *p* value of < 0.05 was considered as statistically significant. Mechanical variables that are mathematically coupled with severity groupings were not formally compared, so no p values are shown (-).The linear regressions graphics of the variables presented in the table are shown in the Supplement.

VILI risk. These factors have consistently been linked to VILI in both experimental and clinical contexts [11–14].

Our study reveals that gas exchange, particularly oxygenation levels that define ARDS severity$_{P/F}$, are not correlated with the key determinants of VILI, as expressed by MPR and DP. While the size of the baby lung—measured via CT as the fraction of well-inflated lung tissue and overall lung gas volume—decreases with both increasing ARDS severity$_{P/F}$ and higher MPR and DP tertiles, oxygenation does not predict VILI risk. This disconnect likely may arise from the fact that oxygenation does not reflect only the anatomical conditions of the lung parenchyma [15], but it is also significantly influenced by vascular factors. These include capillary disruption, microthrombosis [15–18], and the extent of hypoxic pulmonary vasoconstriction [19, 20], as well as haemodynamic factors that affect mixed venous oxygen tension, saturation, and the distribution of pulmonary blood flow between the ventilated and non-ventilated areas (shunt). These factors do not directly correlate with the mechanical stress and strain that contribute to VILI.

For instance, tidal volume alone is a potential injury-inducing factor, but its impact depends on the lung's susceptibility, such as the volume of aerated lung tissue. The actual injury is determined by the ratio of tidal volume to lung volume (strain), making this ratio a critical determinant of VILI. Similarly, the pressure added to the system interacts with lung elastance to determine lung stress, another key factor in VILI development.

Interestingly, our findings show that while smaller baby lungs are associated with higher mechanical power and DP, variables related to CO_2 clearance—like the ventilatory ratio—deteriorate more significantly across MPR and DP tertiles than across ARDS severity$_{P/F}$ classes. This suggests that CO_2 clearance and respiratory mechanics, rather than oxygenation impairment, are more reliable predictors of VILI risk.

These findings suggest that current practices, which tailor therapy intensity based on oxygenation levels, may be misguided. Instead, focusing on respiratory mechanics and CO_2 clearance variables would better reflect the true risk of VILI.

This issue is partly rooted in the historical evolution of respiratory support strategies. Since the 1970s, the primary focus was on maintaining normal oxygenation, using PEEP between 5 and 10 cmH_2O and tidal volumes around 15 ml/kg [21]. In the 1990s, approaches such as the "open lung" strategy [22], high-frequency oscillatory ventilation [23], the prone position [24], and extracorporeal membrane oxygenation (ECMO) [25] were introduced with the same goal.

However, it was not until later that the focus shifted from solely optimizing gas exchange to minimizing VILI by adjusting ventilatory settings, such as adopting low tidal volumes or using ECMO to reduce mechanical power and promoting lung homogeneity through the prone position—independent of their effects on oxygenation. This shift is evident in the latest European Society of Intensive Care Medicine (ESICM) guidelines [26], which recommend continuing prone positioning regardless of its impact on oxygenation. Similarly, in the EOLIA trial, ECMO showed greater benefits in patients with hypercapnia, rather than those with the most severe oxygenation impairment [27] (supplementary figures S33-36). Notably, the ARMA trial revealed that while higher tidal volumes improved gas exchange, they were also associated with increased mortality [28].

Our study highlights a clear dissociation between oxygenation and the risk of VILI. Variables predictive of VILI were similar across different ARDS severity classes based on the P/F ratio, while oxygenation showed little variation across different levels of VILI risk, as defined by MPR and DP. This is significant for clinicians who are guided by recommendations that primarily classify ARDS severity using the P/F ratio. However, linking ventilation strategies solely to oxygenation criteria overlooks the mechanical factors that contribute to lung injury.

This discrepancy underscores the need for a comprehensive re-evaluation of current guidelines, such as those from the American Thoracic Society (supplementary figure S1) [4], which continue to emphasize oxygenation as the primary determinant of respiratory support intensity. Future recommendations should consider selecting respiratory strategies (e.g. prone positioning or extracorporeal membrane oxygenation) based on the risk of VILI, incorporating factors such as respiratory mechanics to balance lung protection with effective oxygenation.

In summary, our findings advocate for a paradigm shift in the management of ARDS, suggesting that therapy should be tailored more closely to respiratory mechanics and CO_2 clearance metrics rather than oxygenation impairment. This approach would align more closely with contemporary understanding of VILI and could lead to improved patient outcomes. The historical evolution of respiratory support, initially focused on oxygenation, has now progressed to emphasize the prevention of VILI based on respiratory mechanics. It is time that clinical guidelines reflect this evolution, moving away from outdated practices and towards strategies that truly mitigate the risk of VILI.

Supplementary Information
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Declarations

Conflicts of interest
None.

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